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Long-Term Outcome of Unrelated Donor Transplantation for AML Using Myeloablative Conditioning Incorporating Pretransplant Alemtuzumab

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ABSTRACT

The outcome of 55 patients who underwent matched unrelated donor (MUD) transplantation for acute myelogenous leukemia (AML) following a conditioning regimen of cyclophosphamide and total-body irradiation (TBI) with the addition of Alemtuzumab 10 mg/kg/day on days −5 to −1 is described. All patients received graft-versus-host diesase (GVHD) prophylaxis with cyclosporine as well as 3 doses of posttransplant methotrexate. Forty-one patients were transplanted in complete remission (CR) (20 in CR1, 20 in CR2, and 1 in CR3), and 14 were not in remission at the time of transplantation as they were refractory to chemotherapy either at induction or at relapse. The group consisted of adult patients with a median age of 37 years. Thirty-five patients were fully matched at HLA-A, -B, -C, and -DRB1. All patients engrafted and there were no cases of graft rejection. Grade II-IV acute GVHD occurred in only 2 patients. Chronic GVHD developed in 30% of patients but was extensive in only 3 cases. The predicted TRM was 11% at day 100 and 26% at 1 year. In multivariate analysis the receipt of an HLA mismatched transplant was associated with a higher transplant-related mortality (TRM) (55% versus 15%). Twelve of the 14 transplant-related deaths were due to infection. The 5-year cumulative incidence of relapse was 36% for the whole group and 28% for patients in CR at transplantation. The 5-year cumulative survival for the whole group was 38% and was 49% for those in remission at transplantation. Seven of the 12 patients transplanted in CR1 with adverse risk cytogenetics remain alive and in remission, and the predicted 5-year overall survival (OS) for this group is 50%. These results support the use of Alemtuzumab for unrelated donor hematopoietic stem cell transplant (HSCT) for poor risk AML in CR1 and for relapsed AML in CR2. The addition of Alemtuzumab is highly effective in preventing both rejection and severe acute and extensive chronic GVHD without an increased relapse risk.

KEY WORDS

MUD • Myeloablative • Campath • Alemtuzumab

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only potential curative therapy for patients with relapsed or poor risk acute leukemia, because both the high-dose chemo/radiotherapy and the graft-versus-leukemia effect (GVL) contribute to disease-free survival. In the absence of a matched related donor, searches of the national and international registries can now identify an HLA-compatible unrelated donor (UD) in up to 80% of patients [1]. However, the high rates of both acute and chronic graft-versus-host disease (aGVHD and cGVHD) observed after UD transplants are responsible for increased toxicity and mortality in these patients, resulting in inferior survival rates compared to transplants from matched sibling donors. Indeed, despite improvements in HLA typing, the rates of grade III-IV aGVHD in fully matched non-T-depleted UD trans-

plant patients still exceed 30% in many large series [2,3]. A number of factors are known to influence the incidence and severity of GVHD, including patient age, degree of HLA-matching, donor sex, cytomegalovirus (CMV) status, and stem cell dose received.

T cell depletion of the graft is the most effective strategy for the prevention of GVHD, but is associated with a higher incidence of graft failure and relapse after HSCT [4]. An alternative strategy is to use pretransplant serotherapy to induce in vivo T cell depletion. The objective is to ensure engraftment of the donor stem cells, and, because of the long half life of the antibodies, to achieve in vivo T cell depletion of the graft and a reduced risk of GVHD. To exploit this effect a number of groups have incorporated antithymocyte globulin (ATG) into their preparative regimens [5-9]. These studies have confirmed that the addition of ATG pretransplant reduces the risk of severe aGVHD, the incidence of extensive cGVHD, and of nonrelapse mortality (NRM) [8-10]. This has led to the results of UD approaching those of matched sibling donor transplants in some series [11-13]. However, there are also disadvantages to this approach because there is evidence for delayed immune reconstitution and a higher risk of infectious complications and of disease relapse [14]. Campath anti-CD52 antibodies can also be utilized for the prevention of GVHD, because the CD52 antigen is expressed on T, B, and NK cells, but not on hemopoietic cells [15]. Campath is effective as GVHD prophylaxis when used for ex vivo T cell depletion of the graft ("Campath in the bag") [16] or by using in vivo Campath pretransplant [6,17].

Here, we report the use of pretransplant in vivo Campath 1H (Alemtuzumab) in a group of 55 adult patients undergoing myeloablative UD transplantation for acute myelogenous leukemia (AML). Our results confirm that this regimen is highly effective at preventing graft rejection as well as severe aGVHD and extensive cGVHD, whereas resulting in long-term survival in approximately 50% of all patients who were in remission at the time of transplant.

PATIENTS AND METHODS

Patients

Between September 1996 and January 2006, 55 consecutive patients (Table 1) with a median age of 37 years received UD HSCT for AML at a single center. The majority of patients had been entered into the Medical Research Council (MRC) AML 10, 12, or 15 trials, and were in complete remission (CR) CR1 (n = 20) or CR2 (n = 20). One patient was in CR3, and 14 patients were not in remission at the time of transplantation as they were refractory to chemotherapy, either at remission induction (n = 12) or at relapse (Table 1). For patients in CR2 the median first remission duration was 0.9 years (range 0.2-2.2). Patients transplanted in CR1 had either adverse risk cytogenetics (n = 12) as defined by the MRC criteria [18] or had intermediate risk cytogenetics and had disease resistant to first-line induction chemotherapy (n = 6), defined by the MRC criteria [19]. In addition 1 case was secondary to myelodysplasia and the remaining patient had biphenotypic leukemia with bone marrow necrosis and no cytogenetic result could be obtained. Of the patients transplanted in CR2 the majority had intermediate (n = 12) or good-risk (n = 6) cytogenetics rather than poor-risk cytogenetics (n = 2) as it was our policy to transplant these cases in CR1. In 34 cases either the patient, the donor, or both were CMV positive. CMV status posttransplant was monitored by weekly qualitative PCR and antigenemia, and patients who reactivated CMV were treated with ganciclovir or foscarnet.

Table 1. *Patient Characteristics*

Age	**36.72 (16.42-57.77)**
Sex: male/female	**22/23**
Remission status of patient at transplant	
• **CR1**	**20**
• **CR2**	**20**
• **CR3**	**1**
• **Not in remission**	**14**
BM cytogenetics	
• **Favorable**	**6**
• **Intermediate**	**27**
• **Unfavorable**	**21**
• **Unknown**	**1**
Donor and recipient CMV seronegative	**21**
$CD34^+$ cell dose $\times 10^6$/kg	**3.57 (1.03-18.6)**
Degree HLA Match at HLA-A, -B, -C, and -DRB1:	
• **Fully matched**	**35**
• **1 antigen mismatch**	**16**
• **2 antigen mismatch**	**4**

Data are median (range).
CMV indicates cytomegalovirus; CR, complete remission.

Thirty-four patients received bone marrow (BM) and 21 received granulocyte-colony stimulating factor (G-CSF) mobilized peripheral blood stem cell transplantation (PBSC). Since 1999, PBSC was requested for all patients; however, the final choice between BM and PBSC was decided by the donor in conjunction with the UD registry policy. During this period 21 of 45 (47%) transplants were from PBSC. For patients receiving PBSC, a total of $\geq 4 \times 10^6$/kg $CD34^+$ cells were requested, and for patients receiving BM, a total mononuclear cell count of $\geq 3 \times 10^8$/kg was requested.

Histocompatibility

Donors were recruited from the Anthony Nolan Trust (n = 39) and British Bone Marrow Registries

(n = 3), and where necessary, the European and American Registries (n = 13). The methods of tissue typing have changed over the past 10 years, and consequently, the resolution obtained prior to transplantation has also changed over that time. In view of this, a comparison of outcomes based solely on the original tissue typing data seemed inappropriate. For the majority of patients we were able, however, to obtain retrospective high-resolution results (to 4 digits) from the Anthony Nolan Trust for the HLA-A, -B, -C, and -DRB1 alleles, and therefore, only matching at these loci was considered in this analysis. When the retrospective high-resolution data was included, 80% of the pairs in our analysis had high-resolution typing performed at HLA-A, -B, -C, and -DRB1. All of the mismatches identified at these loci were antigenic, except in 1 pair with a B and C mismatch, where the C was an antigenic mismatch and the B alleleic. In the remaining cases, the tissue typing was a mixture of medium and low resolution. Only 2 pairs had low-resolution typing alone, and in both cases mismatches were identified. In 35 cases the patient and donor were fully matched at HLA-A, -B, -C, and -DRB1. A total of 16 patients received a 1-locus antigen mismatched transplant at HLA-A (n = 10), HLA-C (n = 5), and HLA-DRB1 (n = 1). Four patients received transplants mismatched at 2 loci.

Conditioning Regimen and GVHD Prophylaxis

All patients received an identical conditioning regimen comprising total body irridiation (TBI) 14.4 Gy in 6 fractions over 3 days and cyclophosphamide (60 mg/kg × 2). In addition, all patients received pretransplant immunosuppression with Alemtuzumab, 10 mg/day, days −5 to −1 (total dose 50 mg). For additional GVHD prophylaxis all patients received Methotrexate (10 mg/m^2) on days +1, +3, and +6 and Cyclosporin A was administered from day −1 at a dose of 2.5 mg/kg by mouth to maintain a blood level of 150-250 ng/nL. In the absence of GVHD, cyclosporine was tapered from day 50 with the aim to discontinue therapy by 6 months.

Definitions

Acute GVHD was graded 0 to IV according to standard criteria [20]. Patients dying before day 30 posttransplant were excluded from the analysis of aGVHD. cGVHD was assessed in patients surviving >90 days from the time of transplant and was defined as limited or extensive [21]. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of 0.5×10^9/L or above. Platelet engraftment was defined as the first of 7 days with platelet counts of 20×10^9L or above without transfusion.

Statistics

Statistical analysis was performed using SPSS (v.9.0) software (SPSS Inc., Chicago, IL) and "R" software (R Development Core Team [2006], R Foundation for Statistical Computing, Vienna, Austria). The probabilities of overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier method, comparing the groups using the log rank test. Estimation of the cumulative incidence curves with subgroup analysis by the Gray method was utilized to analyze transplant-related mortality (TRM), relapse risk, and the incidence of and aGVHD and cGVHD [22]. Multivariate analysis of factors affecting TRM and relapse risk was performed using Fine-Gray analysis [23]. In the univariate analyses for OS, TRM, and relapse the following factors were considered using the log rank test: Stem cell source (BM versus PBSC), patient age above or below the median, remission status, presence of aGVHD, presence of cGVHD, CMV status, transplanted CD34 count above or below the median, cytogenetic risk group, and HLA matching status. For the univariate analyses of factors affecting the development of aGVHD and cGVHD, donor sex, stem cell source, patient age, remission status, transplanted CD34 count, and HLA matching status were considered. In addition, aGVHD was considered as a risk factor for cGVHD.

RESULTS

The data were analyzed on April 5, 2006. Twenty-four patients remained alive on this date, with a median follow-up of 4.7 years (range 0.5-9.2).

Engraftment and CMV Reactivation

Fifty-one of 52 evaluable patients achieved sustained donor engraftment. The remaining patient failed to recover her platelet count prior to her death from pneumonia at 8 months posttransplant. This patient, however, developed anti-HPA antibodies against her donor's platelets and a bone marrow examination at 2 months posttransplant demonstrated the presence of megakaryocyte engraftment. The median time to neutrophil engraftment of $>0.5 \times 10^9$/L was 14 days (10-26) and for platelet engraftment of $>20 \times 10^9$/L was 16 days (11-40). Sixteen of the 34 patients with the potential to reactivate CMV did so posttransplant, as assessed by in-house qualitative PCR and antigenemia assays. The median number of episodes of CMV reactivation was 1 (0 to 4). One of these patients died of CMV pneumonitis despite treatment with ganciclovir and foscarnet. None of the others went on to develop CMV disease.

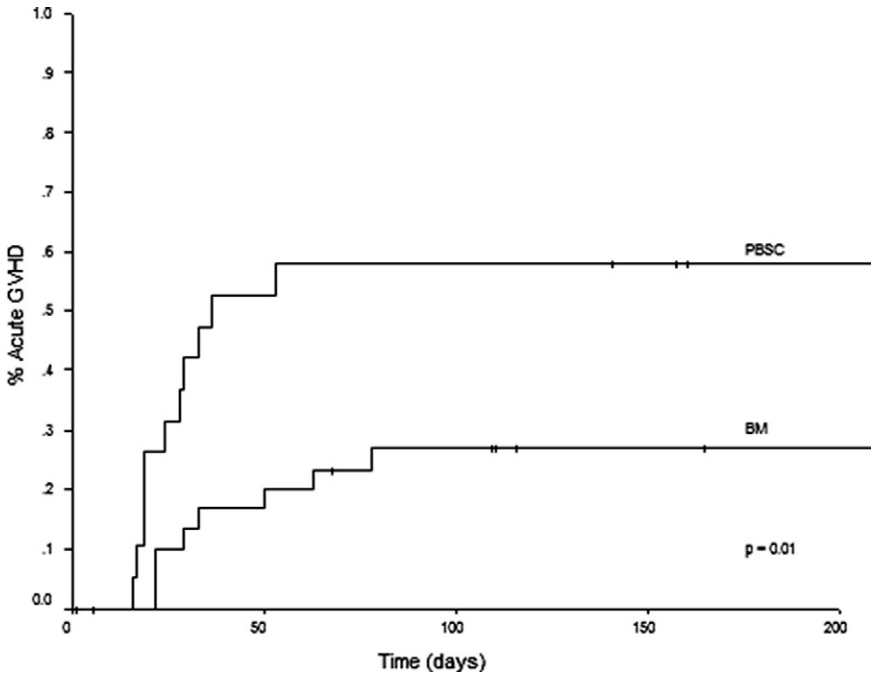

Figure 1. The development of acute GVHD by cell source. The receipt of PBSC was associated with the development of acute GVHD.

aGVHD and cGVHD

Nineteen of 53 evaluable patients developed aGVHD. In 17 patients this was grade I, and clinically significant GVHD was seen in only 2 patients (1 grade II and in 1 grade IV). The 1 patient who developed grade IV aGVHD was mismatched at both HLA-A and HLA-C loci, and was in relapse at transplant. The only factor associated with a higher incidence of aGVHD was the receipt of PBSC as opposed to bone marrow derived stem cells ($P = .01$; Figure 1). The presence of an HLA mismatch did not significantly have an impact on the development of acute GVHD ($P = 0.47$).

Fourteen of 42 evaluable patients developed cGVHD, and the cumulative incidence of cGVHD was 30%. cGVHD was limited in 11 cases and extensive in 3 cases. Six of the 14 patients were recipients of PBSC and the remaining 8 received BM. The median time to the onset of cGVHD was 175 days (range 105-244 days) after transplantation. Five patients were diagnosed with GVHD after their cyclosporine was discontinued. Three of these had limited GVHD and were managed with a combination of topical steroid and short courses of oral steroids. The remaining 2 had more extensive disease requiring the reintroduction of cyclosporine with oral steroids. The only risk factor that predicted the development of cGVHD on univariate analysis was the occurrence of aGVHD ($P = .004$).

TRM

Fourteen patients died from transplant-related causes between 2 days and 1.6 years posttransplantation. Of these, 12 patients died from infection (respiratory syncytial virus n = 3, influenza A n = 1, CMV n = 1, PCP n = 1, methicillin resistant staphylococcus aureus n = 1, Candida Glabrata n = 1, and 4 cases of pneumonia in which no organism was identified). In addition, 1 patient died from aGVHD and 1 from autoimmune hemolysis. The predicted TRM at day 100 was 11% and at 1 year was 26%. The predicted TRM of the whole group at 5 years was 27%. The 5-year probability of TRM was 55% for patients with any degree of HLA mismatch compared to 15% for

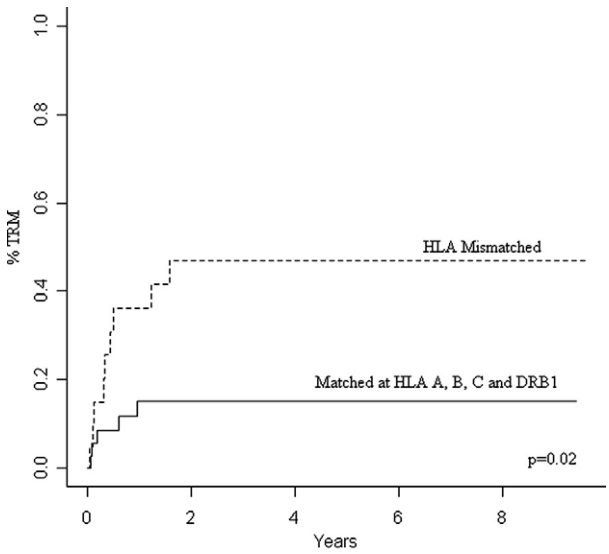

Figure 2. The effect of HLA match on TRM. Patients who were fully matched at HLA-A, -B, -C, and -DRB1 had a significantly lower TRM than those with any degree of HLA mismatch.

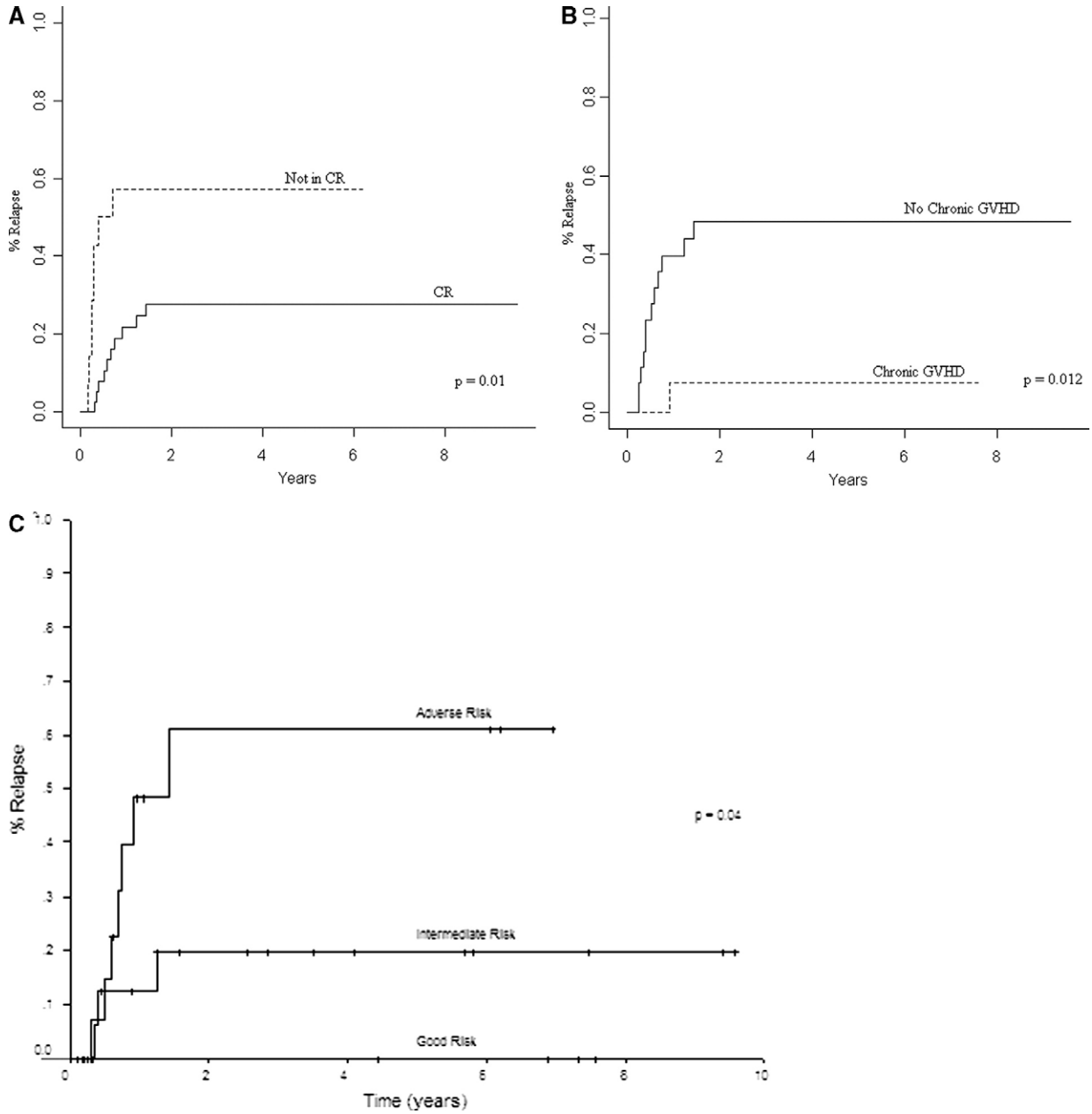

Figure 3. Effect of Remission Status at Transplant on Relapse (A); Patients who were not in remission at the time of transplantation were significantly more likely to relapse than those transplanted in remission. The Effect of Chronic GVHD Post-Transplant on Relapse (B); The presence of chronic GVHD protected against relapse. The Effect of Cytogenetic Risk Group on Relapse for Patients in CR at Transplantation (C); Cytogenetic risk group predicted for relapse in patients who were in remission at the time of transplantation.

those transplanted from an HLA-A, -B, -C, and -DRB1 matched donor ($P = .02$; Figure 2). In multivariate analysis, the degree of HLA match remained the only significant factor affecting TRM. Although patients above the median age at transplant tended to have a higher TRM, this was not significant in the univariate ($P = .08$) or multivariate ($P = .06$) analyses.

Relapse

Eighteen patients have relapsed at a median of 146 days (range 66-524 days). The 3- and 5-year cumulative incidence of relapse were both 36%. The 5-year cumulative incidence of relapse for patients in remission at the time of transplantation was 28% compared to 57% for those not in remission ($P = .01$; Figure 3A). The 5-year probability of relapse for patients in CR1 was 42% compared to 16% for those patients in CR2 ($P = .07$). The presence of aGVHD did not have an impact on the probability of relapse; however, the development of cGVHD protected against relapse ($P = .012$; Figure 3B). The 5-year probabilities of relapse for patients in remission at the time of transplan-

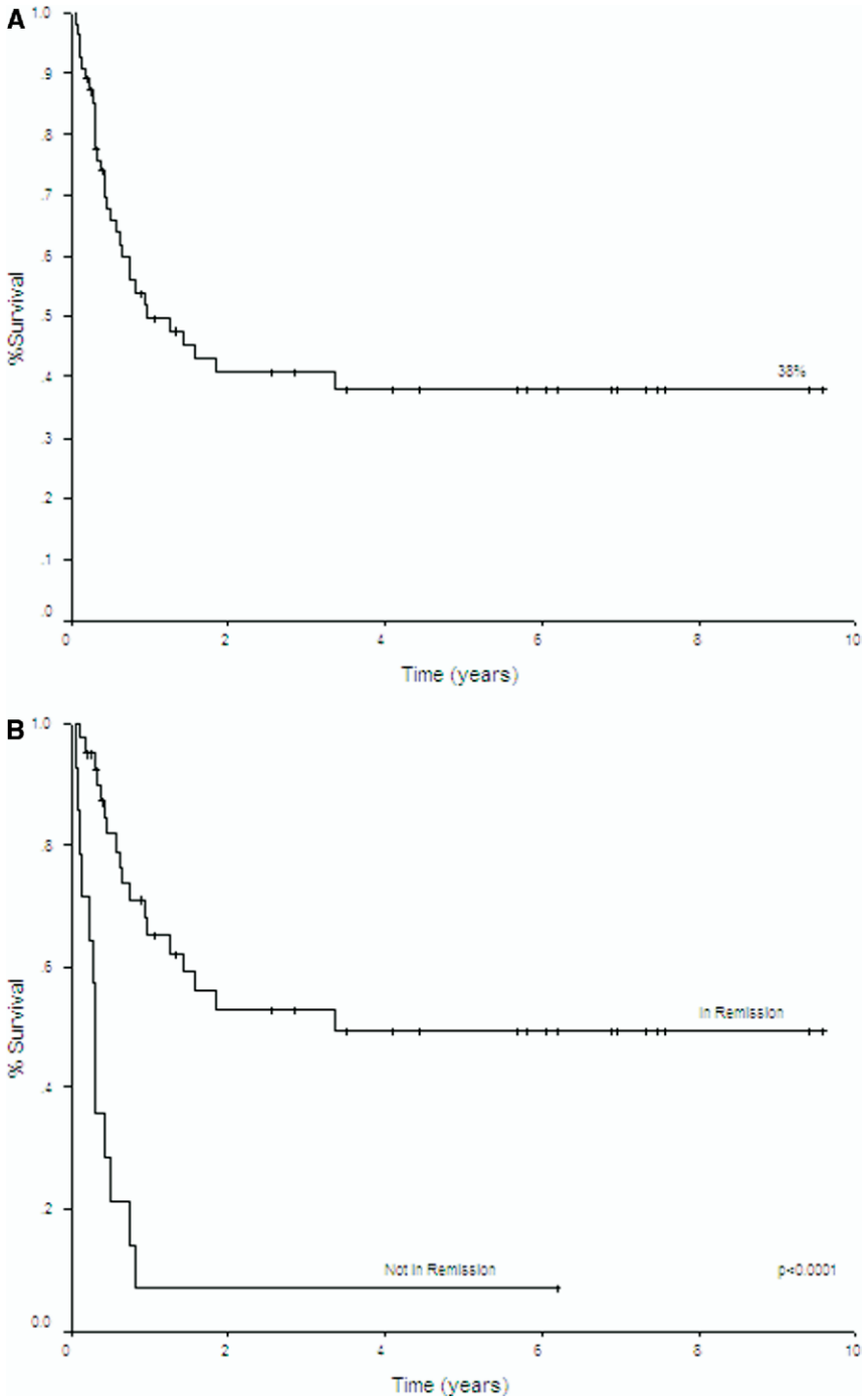

Figure 4. Overall survival of the whole group (A). The effect of remission status at the time of transplantation on OS (B). Patients who were transplanted in remission had a significantly better OS. The Effect of HLA match on OS (C). Patients who were fully matched at HLA-A, -B, -C, and -DRB1 loci had a trend toward better OS.

tation with good, intermediate, and adverse risk cytogenetics were 0%, 21%, and 51%, respectively ($P = .06$; Figure 3C) In multivariate analysis, 2 factors—remission status at transplant ($P = .04$) and cytogenetic risk group ($P = .04$)—affected the probability of relapse. Of the 12 patients with adverse risk cytogenetics who were transplanted in CR1, 5 have relapsed.

Survival

The 5-year cumulative survival for the whole group was 38% (Figure 4A). For those in CR, it was 49% compared to 7% for those not in CR at transplantation ($P < .0001$; Figure 4B). No other factor had an impact on OS. Despite the fact that HLA mismatch

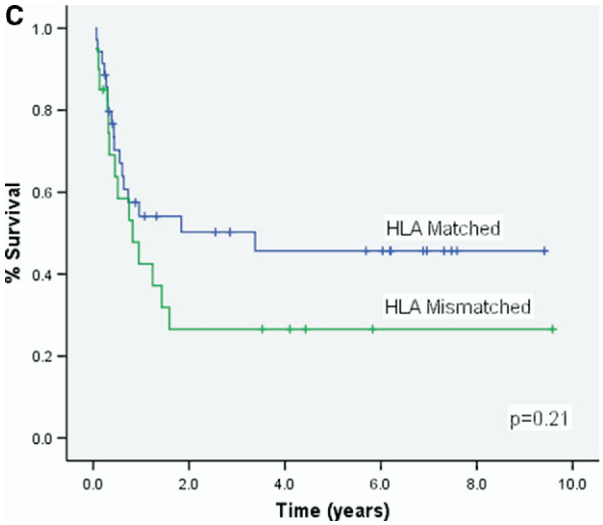

Figure 4. (continued)

was associated with a higher TRM, this did not translate to a significant reduction in OS, although there was a trend toward a worse outcome in the HLA mismatched group (Figure 4C). We also analyzed factors affecting the survival of 40 patients in CR at transplantation. No one factor was identified on univariate analysis that significantly had an impact on OS in this group of patients. Of the 12 patients with poor risk cytogenetics who were transplanted in CR1, 7 remain alive, 5 of whom are over 1 year posttransplant including 3 patients who are over 6 years posttransplant. The predicted 5-year OS for these patients is 50%.

DISCUSSION

The role of UD transplantation in AML remains controversial, primarily because of the toxicity and mortality reported from high rates of both aGVHD and cGVHD. Our policy has been to consider high-risk AML patients in CR1 and patients in CR2 (excluding FAB type M3) for UD HSCT. Our strategy to prevent GVHD and graft rejection has been to use pretransplant in vivo Alemtuzumab to induce T cell depletion in the recipient. We have previously reported this approach to be as effective as combined pre- and posttransplant Campath therapy [6]. Here we present mature outcome data relating to 55 patients transplanted for AML from a UD after standard cyclophosphamide and TBI-based conditioning with the addition of pretransplant Alemtuaumab.

In agreement with our previous report [6], pretransplant Alemtuzumab was highly successful in preventing both rejection and severe aGVHD and extensive cGVHD. We observed no cases of graft rejection, and although aGVHD developed in 19 patients, this was restricted to grade I in 17 cases and grade II in another case. The single case of grade IV aGVHD in this study received a transplant that was mismatched at both the HLA-A and -C loci. cGVHD developed in 14 cases but was only extensive in 3, and the development of aGVHD or cGVHD did not have an impact on OS. Although posttransplant methotrexate was used as additional GVHD prophylaxis in these patients it is not clear given the low rate of GVHD that this is necessary, and our current policy is to omit this treatment in high-risk patients. Most nonrelapse deaths resulted from infection, suggesting that although Campath was highly effective at preventing GVHD following mismatched transplants, these patients had slow immune reconstitution leading to a risk of posttransplant infections.

This article also highlights the importance of high-resolution HLA typing to avoid mismatches that may remain unrecognized when only medium- or low-resolution typing methods are used. For patients fully matched by high-resolution typing at HLA-A, -B, -C, and -DRB1 the predicted TRM at 5 years was only 15% compared to 55% for patients with a mismatch. This was also reflected as a trend toward a poorer OS, although this did not reach significance. Other recent studies have shown the importance of allele level typing to identify "hidden mismatches" to improve the outcome of UD transplantation [2,3,24,25]. These studies all suggest (whether T cell depleted or T cell replete) that mismatched pairs have a higher incidence of transplant complications. Even with a 10/10 matched donor the incidence of GVHD in T cell-replete transplants exceeds that of T cell-deplete transplants. One difference appears to be that single mismatches may be tolerated with regard to OS in T cell-depleted transplants (where this is not reported to be the case with T cell-replete transplants). However, as can be seen in this study, there is evidence that even in T cell-depleted transplants the TRM is higher in mismatched pairs.

The use of T cell depletion might be expected to have a negative impact on disease relapse [4]; however, for patients in CR at transplant the relapse risk was 28% and the risk of relapse was related to the cytogenetic risk group and remission status at transplantation. Despite this, for the 12 patients with poor-risk cytogenetics who were transplanted in CR1, the predicted 5-year OS is 50%. Although not significant, the probability of relapse for patients transplanted in CR2 was lower than for those transplanted in CR1. This was a surprising finding, as the reverse situation might have been expected based on other reported series [26,27]. The finding probably reflects the cytogenetic spread of patients between the 2 groups. Patients transplanted in CR1 included 7 intermediate- and 12 poor-risk patients with no good-risk patients. Those transplanted in CR2 included 6 good-risk, 12 intermediate-risk, and only 2 poor-risk patients. The re-

lapse risk for patients not in CR at transplant was high (>80%) in keeping with previous observations [26,28].

It is difficult to compare our results with other series of UD HSCT for AML, as almost half the patients in our group were over the age of 40 years. Other published series have reported median ages of at least 10 years lower [17,29,30]. Increasing age is a risk factor for TRM in patients receiving conventional allografts as treatment for AML [31,32]. The fact that this was not reflected in this series may be related to the higher age of the group as a whole.

An alternative method of transplanting these patients would have been to use a reduced intensity conditioning (RIC) regimen, an approach that has been used by a number of groups. Wong et al. [33] have reported the use of fludarabine- and melphalan-based regimens that included ATG in the preparative regimen. They undertook 29 MUD transplants including 16 for patients with AML or high-risk myelodysplastic syndromes (MDS). Their estimated OS and progression-free survival (PFS) rates at 1 year were 38% and 34%, respectively. Their rate of grade II to IV aGVHD was 41%. Eight of 16 evaluable patients developed extensive cGVHD. Martino et al. [34] have reported the use of a fludarabine and busulfan regimen in the context of HLA-identical sibling transplantation for 37 patients with AML or high-risk MDS. Although they had a short median follow-up of 297 days, their 1-year incidence of TRM was only 5%, with a 1-year PFS of 66%. In a larger study of 76 patients with high-risk AML or MDS who received an allograft using a fludarabine/melphalan RIC regimen incorporating Alemtuzumab, the day 100 TRM was only 9%, and no patient developed greater than grade 2 GVHD [35]. The 3-year OS and disease-free survival (DFS) for patients with AML in CR at the time of transplantation were 48% and 42%, respectively, and the risk of disease relapse at 40% was the most common cause of treatment failure. Taken together, none of the OS figures in these reports are superior to those reported here. In a direct comparison of transplant outcome in 150 patients with MDS or AML transformed from MDS receiving either matched related donor (MRD) or MUD transplants using myeloablative or nonmyeloablative conditioning regimens, Scott et al. [36] have shown similar OS and PFS for the 2 types of conditioning. In a larger study from the European Blood and Marrow Transplant, the outcomes of 722 patients over the age of 50 years with AML who received either an RIC or a myeloablative conditioning regimen in an HLA identical sibling setting were compared [37]. A significant reduction in cGVHD and NRM was noted in the RIC group, but the relapse rate was significantly higher and there was no difference in the 2-year RFS/OS between the 2 groups. The long-term benefits of RIC regimens in comparison to conventional myeloablative regimens remain to be clarified, and no disease-specific prospective trials comparing the results of RIC with myeloablative HSCT have been published. The use of pretransplant Alemtuzumab in our regimen has enabled us to undertake myeloablative transplantation with a reduced incidence of GVHD and day 100 and 1-year TRM of 11% and 26%, respectively, and in patients with a matched donor our results support the use of myeloablative conditioning regimens as the treatment of choice.

The alternative treatments to UD HSCT for these patients include chemotherapy alone or an autograft. For poor-risk patients in CR treated with chemotherapy alone in the MRC AML10 trial, the 5-year OS and relapse rate was 17% and 75%, respectively [19]. Similarly, the EORTC-GIMEMA group reported an EFS of 12% and relapse risk of 87% [38]. We only had 12 patients in this series with poor risk cytogenetics who were transplanted in CR1. Accepting the selection bias in our group who were fit enough for a UD HSCT, we feel that the 50% OS following this Alemtuzumab-containing regimen is encouraging. For patients in CR2 without a sibling donor the other options available are an autograft or chemotherapy. A study from the MRC AML10 and 12 trials has shown that MUD transplant and autograft are significantly superior to chemotherapy in this patient group, with an OS of 40%, 33%, and 22% at 5 years and a relapse risk of 38%, 59%, and 71% for UD transplants, autografts, and chemotherapy, respectively [39]. Our study demonstrated a 5-year OS of 51%, with a 20% risk of relapse for patients in CR2; results are comparable to those that can be achieved with sibling transplantation. We propose that these data support the use of UD HSCT in AML in CR2 for those patients lacking a sibling donor.

In summary, our results demonstrate the efficacy of pretransplant Alemtuzumab in reducing GVHD and rejection in patients undergoing UD HSCT for poor risk AML in CR1 and for relapsed AML in CR2 who have a donor matched at HLA-A, -B, -C, and -DRB1. Furthermore, as patient age had no effect on OS, older patients up to 50 years are suitable for this approach. For patients not in remission at the time of transplantation the results were poor, and other strategies not involving in vivo T cell depletion are needed.

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